Today's Treatment

Blood and Neoplastic Diseases

Myeloproliferative Disorders

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The reticulum cell is thought to be the haemopoietic precursor cell from which originate the erythrocyte, the granulocytic leucocyte, and the megakaryocyte (and platelets). Uncontrolled proliferation of these cell lines or of the reticulum cell itself gives rise to several diseases or syndromes; these have, by convention, been divided into the leukaemias and the non-leukaemic myeloproliferative disorders. In the latter group are included polycythaemia vera, myelosclerosis, essential thrombocythaemia, and some other rare diseases. It is useful to retain the concept of "myeloproliferative disorders" as the different conditions may co-exist or may merge into each other, and occasionally some time may elapse before a bone marrow showing a myeloproliferative picture will alter sufficiently to indicate which cell line has been especially or specifically affected.

Some of the disorders may run a relatively benign course which does not alter throughout the life of the patient. In other cases the disease may become malignant, sometimes only after a considerable period, but it may run an acute course from the beginning. Leukaemia or myelosclerosis may follow polycythaemia, but occasionally patients may present with clinical features of both leukaemia and polycythaemia and there are even examples of polycythaemia developing after successful treatment for leukaemia. This sequence of events occurs even more commonly in myelosclerosis; this is usually a chronic disease but occasionally it may present as an acute leukaemia and have a rapid course leading to a fatal end. The interrelationship of the myeloproliferative disorders is illustrated in the figure.

Polycythaemia Vera

In polycythaemia vera there is an absolute increase in the red cell volume. As a rule this results in a high red cell count, haemoglobin, and packed cell volume—though these blood count changes are not invariable. Polycythaemia vera is commonly associated with a leucocytosis, thrombocytosis and enlargement of the spleen. Though as a rule diagnosis is fairly simple it is necessary to distinguish polycythaemia vera from two other forms of polycythaemia. The first of these is relative ploycythaemia, in which the apparent increases in red cell and packed cell volume values are due to decreased plasma volume and not to an increase in red-cell volume. The second is secondary polycythaemia, in which there is an increased red-cell volume which may be due to the stimulus of anoxia caused by defective oxygen saturation of the blood (as occurs in congenital heart disease or certain pulmonary diseases) or by the presence of an abnormal or inert form of haemoglobin. Secondary polycythaemia may also be associated with renal lesions, especially carcinoma of the kidney, and with several other tumours, such as uterine fibromas and hepatomas.

When the diagnosis of polycythaemia vera is established the doctor has to decide on the therapeutic approach, the aim of which is to achieve a prolonged reduction of the red-cell volume to more or less normal levels. This may be accomplished by (1) venesection, (2) chemotherapy, and (3) radiotherapy.

VENESECTION

Venesection reduces the blood volume rapidly and thus produces quick symptomatic relief. In many patients, however, it may have only a transient effect and lead to gross iron deficiency with as severe a polycythaemia as previously. Furthermore, thrombocytosis is not reduced and may even become more pronounced. Another drawback is that venesection may be technically difficult when the blood viscosity is markedly raised. Nevertheless, venesection has a place in the treatment of polycythaemia vera, especially in young patients, when the disease is benign, when rapid reduction of the blood volume is required as, for example, before surgery, and when the platelet count is particularly low.

CHEMOTHERAPY

The most commonly used drugs at present are busulphan and chlorambucil. Cyclophosphamide, pyremethamine, and phenylalanine mustard are also sometimes used. These may be administered intermittently in short courses, but additional maintenance therapy may be required to achieve significant remission. Thus, for example to induce a remission, busulphan is usually given in a dose of 4-6 mg daily, chlorambucil 6-8 mg daily, and cyclophosphamide 100-150 mg daily—each over a period of 4-6 weeks. For maintenance therapy about half the induction dose is given, but the exact amount must be assessed individually for each patient. Though a significant remission rate has been claimed for all these agents, none appears to be entirely satisfactory. Prolonged treatment is necessary, requiring close supervision and frequent blood counts. Unmaintained remissions last for about five to six months and maintenance therapy is often difficult to control, as severe thrombocytopenia and toxic side effects may occur.

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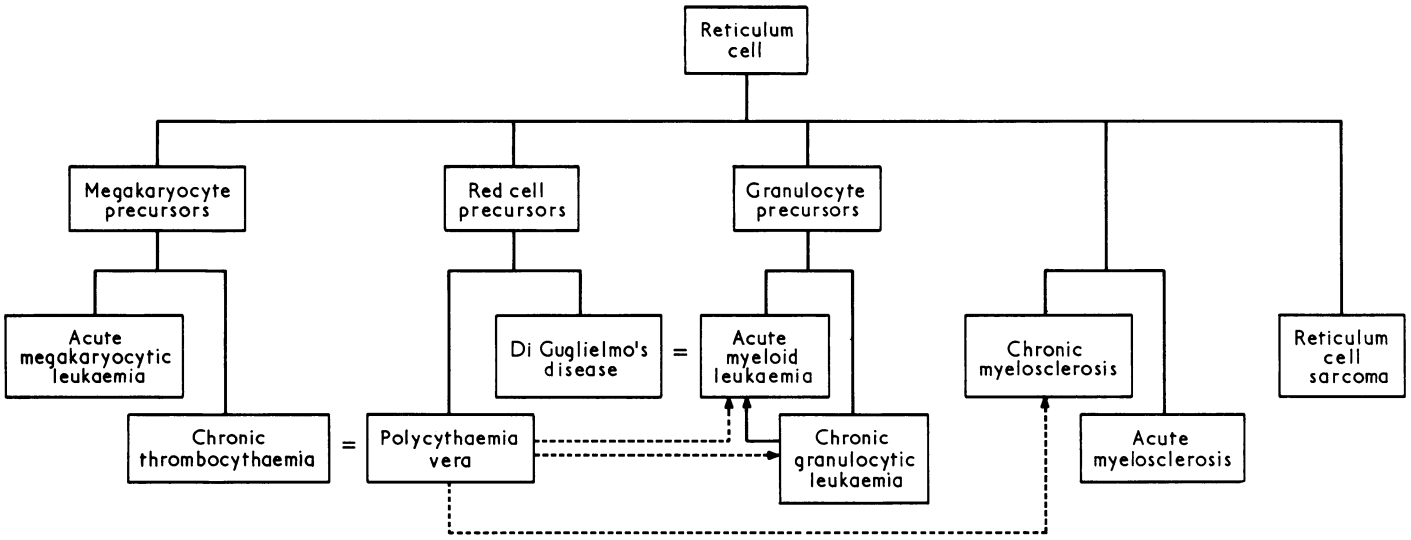

Suggested relationships of myeloproliferative disorders.

RADIOTHERAPY

Previous radiotherapeutic methods were replaced when radioactive phosphorus (^{32}P) was introduced, and over the last 30 years it has become the commonest agent for the treatment of polycythaemia vera. The dosimetry of radiophosphorus is empirical, primarily because it is not possible to estimate the amount of erythropoietic tissue in an individual patient; as a rule, the usual dose is between 4 and 7 mCi and it is administered intravenously. The actual dose will take into account the patient's weight and the severity of the polycythaemia as judged from the red-cell volume. It is preferable, but not essential, that the patient should be in hospital for a day or two to ensure that urine and any contaminated linen are subjected to special radiation protection. The urine voided in the first eight hours contains the greatest amount of radioactivity.

The patient should be seen at suitable intervals after treatment. The platelets and leucocytes usually fall to their lowest levels three-five weeks after the injection, whereas the fall in red-cell count becomes apparent only after six-eight weeks. Because of this, treatment is not repeated for at least three-four months. When a remission is achieved, the patient needs to be seen only at three-monthly intervals. A decision to re-treat is based on the clinical and haematological findings, and the dose of ^{32}P to be administered is assessed in the light of these features and the extent of the previous response.

About 85% of patients achieve complete haematological and clinical remission and about three-quarters of these require only a single injection. A very few patients (about 5%) are particularly and persistently resistant to treatment with radiophosphorus and in these venesection or chemotherapy is to be preferred. The length of remission varies considerably but on average is about 22-24 months and characteristically an individual patient will for many years have the same response and duration of remission after each successive treatment.

One possible disadvantage of the use of radiophosphorus is that it may cause or increase the incidence of leukaemia or myelosclerosis. In our own experience in a series of 200 cases followed for at least five years, myelosclerosis has occurred in 21 patients, acute myeloblastic leukaemia in eight, and chronic granulocytic leukaemia in one. Other workers have reported a relatively higher incidence of leukaemia, but differences in diagnostic criteria and follow-up make it difficult to compare various reported series. The relation of these complications to treatment is difficult to assess, as they may occur also in untreated patients, and myelosclerosis especially appears to be a natural termination of the disease provided the patient survives long enough. On balance at present the advantages of radiophosphorus outweigh the risk, and it is the treatment of choice in most cases.

Essential Thrombocythaemia

In thrombocythaemia, a condition closely related to polycythaemia vera, the platelet count is increased to over 1 million/μl. Thrombosis and haemorrhage are common and the increase in the platelet count dominates the clinical and haematological picture. Treatment is directed to reducing the platelet count either by radioactive phosphorus or chemotherapy. If successful, it will generally, though not invariably, control and prevent haemorrhagic and thrombotic episodes. Response to radiophosphorus is similar to that in polycythaemia vera except that the period of remission may be shorter, and good response may be obtained with a dose of about 4-5 mCi. Busulphan and chlorambucil are about equally efficacious and are of particular value when remission is short and maintenance therapy necessary. In some cases a fall in the platelet count, which results in control of haemorrhage, is followed by an increase in red-cell volume to a polycythaemic level.

Myelosclerosis

In myelosclerosis the essential pathological feature of the marrow is proliferation of fibrolasts with deposition of collagen and frequently an increase in osseous tissue. This may occur also in certain other conditions such as tuberculosis or malignant disease and it is, of course, important to exclude these when making the diagnosis of primary myelosclerosis. Not infrequently in myelosclerosis there is a history of preceding polycythaemia. Treatment of myelosclerosis depends on several factors. These include the stage of development of the disease; the degree of anaemia, and whether there is severe thrombocytopenia or leucopenia, or both; the presence of extramedullary haemopoiesis; and the role of the spleen.

In some cases the disease progresses very slowly, the blood picture remaining relatively stable with but a minor or moderate degree of anaemia, and the spleen enlarges only very gradually. In such cases, there are few if any symptoms and the patient can lead a normal or almost normal life without treatment. Eventually the patient will develop symptoms due to anaemia, splenic enlargement, bleeding (which is fre-

quently gastrointestinal), or the constitutional effects of the disease. On the other hand, some patients present initially with significant symptoms and require treatment at an early stage. The commonest causes of death are marrow failure, infection, and cardiac or renal failure. About 10-20% die with an acute termination which is similar to acute myeloid leukaemia. The disease is incurable and treatment is essentially palliative, aimed at relieving symptoms and maintaining the patient in a haematologically normal state for as long as possible. Several lines of treatment may be considered, as follows:

SUPPORTIVE MEASURES

Supportive measures include blood transfusions to maintain the haemoglobin at a level of around 10 g/dl, platelet transfusions to control haemorrhagic episodes, supplementary iron, analgesics, and sedatives. Hyperuricaemia and the associated complication of gout are frequent and should be controlled with allopurinol. As most patients with myelosclerosis develop folate deficiency with megaloblastic change at some stage during their disease, folic acid (5 mg daily) should be given to patients who are anaemic. Occasionally, the thrombocytopenia which occurs in myelosclerosis is associated with the folate deficiency and may thus also respond to folic acid.

CORTICOSTEROIDS

High doses of prednisone (40-60 mg per day) are usually administered when transfusion requirements increase and there is significant haemolysis or bleeding associated with thrombocytopenia. Nevertheless, treatment with this drug carries risks and should be relatively short and abandoned if there is no early sign of effective response.

ANDROGENS

The mechanism of the action of androgens in myelosclerosis is not clear. There is evidence that erythropoiesis is improved and the red-cell mass is increased and some workers have suggested that it may be due to a reversal of fibrosis. The most commonly used preparation has been testosterone enanthate, in doses of 300-600 mg weekly by intramuscular injection, continued for at least three-four months. More recently, the anabolic steroid oxymetholone has been used and is favoured because of the reduced incidence of side effects. The usual dose is 2-3 mg/kg daily, administered by mouth. Nevertheless, its value in myelosclerosis has not yet been fully assessed, though we have had occasional gratifying results. In our own experience, one patient even became erythraemic again, and required venesection for symptoms due to an increased red cell mass.

CHEMOTHERAPY

By far the commonest cytotoxic agent used is busulphan. This is usually employed in cases with appreciable splenomegaly, the aim being to achieve a reduction in the size of the spleen or halt the progress of the disease, but avoiding significant suppression of erythropoiesis or a dangerous fall in the leucocyte or platelet count. If the patient has leucopenia or thrombocytopenia, this precludes the use of the drug. The dose is about 2-4 mg daily, but this should be adjusted in the light of the response of the individual patient. Owing to the danger of haemopoietic depression, busulphan must be given only under careful haematological control. Some reports have claimed very satisfactory results in a small proportion of patients.

SPLENIC IRRADIATION

Splenic irradiation has a small but definite part to play in the management of myelosclerosis. The main aim is to reduce the size of an appreciably enlarged spleen and thus to relieve symptoms due to pressure and to a lesser extent the associated constitutional symptoms. Usually only the lower half of the spleen is irradiated and a dose of about 1,000-1,500 rads is given over two-three weeks. Radiotherapy abolishes haemopoiesis in the treated area and must be carried out under careful haematological control because of the risk of leucopenia or thrombocytopenia. In most patients there is a fall in the haemoglobin level and packed cell volume over the next one-three months but it is rarely severe—while occasionally the opposite may occur, presumably owing to a reduction in the splenic red-cell pool and possibly also to a decrease in the rate of red-cell destruction. Most patients benefit from a course of splenic irradiation but the period of relief tends to get progressively shorter. Radiotherapy (and also chemotherapy) may aggravate the hyperuricaemia so that appropriate treatment for this may be required.

SPLENECTOMY

There is as yet no general agreement on the value and indications for splenectomy. This is partly because of the different criteria used by various workers.

The operation involves certain risks, especially as the patients are usually old, in poor general condition, and may have been on corticosteroid therapy for long periods. Moreover, the spleen is often grossly enlarged and its removal is technically difficult. In these circumstances postoperative mortality and morbidity due to bleeding, embolism, and infection are high. In the earlier stages of the disease, especially in patients with a normal or high platelet count, the operation may be followed by thrombocytosis and an increased tendency to thromboembolism. Furthermore, there is no evidence that splenectomy has any influence on the natural history of the disease. Nonetheless, splenectomy may be of considerable value in a selected group of patients. When there is considerable splenomegaly, the spleen acts as a site of red-cell pooling and is responsible for an increased plasma volume. In addition, there may be haemolysis with appreciable red-cell destruction by the spleen. Both these factors may play a paramount part in causing clinical anaemia, and splenectomy may reduce or entirely eliminate the need for transfusion over varying periods, thus allowing the patient to lead a normal life. Furthermore, in cases with considerable thrombocytopenia the removal of a massive spleen which may contain up to 90% of the platelets may result in a normal platelet count and abolish bleeding.

It is important to distinguish the cases where the role of the spleen is primarily that of an organ of red-cell destruction, from those cases where the spleen because of extramedullary haemopoiesis is the major organ of erythrocyte production and in which splenectomy would be harmful. Erythrokinetic studies using ^{51}Cr for red-cell survival, ^{59}Fe for identifying the sites of erythropoietic activity and ^{99m}Tc for measuring splenic red-cell mass can help to select suitable patients. If the short-lived isotope of iron (^{52}Fe) is available, the distribution of erythropoietic tissue in the body can be assessed. Nevertheless, even when isotope studies show that the spleen is an important erythropoietic organ this need not preclude the operation, because, as a rule, the liver takes over as the main site of extramedullary erythropoiesis.

Some have suggested that splenectomy should be performed in every patient as soon as myelosclerosis is diagnosed. This approach might be considered extreme and the most rational approach is to assess each case on the basis of symptoms, haematological, biochemical, and erythrokinetic findings, and the rate of progress of the disease.

Malignant Myelosclerosis

Malignant myelosclerosis is a variant of myelosclerosis, to which it is related in a way similar to that of acute myeloblastic to chronic granulocytic leukaemia. The condition pre-

sents in an acute form from the beginning and runs a fairly rapid downhill course with severe anaemia, leucopenia, and thrombocytopenia. It can often, though not always, be distinguished from the acute terminal phase of chronic myelosclerosis, as it has a peripheral blood picture similar to leukaemia and a bone biopsy appearance of chronic myelosclerosis. Survival time is short, usually a few months, and death is caused by anaemia, haemorrhage, or intercurrent infections. It seems to be refractory to treatment and only supportive measures have any value.

Any Questions?

We publish below a selection of questions and answers of general interest

Nocturnal Teeth Grinding

What advice can be given about nocturnal teeth grinding? A woman with this problem finds her marriage in danger.

This appears to be a severe case of bruxism, which may take the form either of static clenching of the teeth or of active grinding. Bruxism is usually associated with stress or anxiety. More rarely it may arise from organic lesions within the brain or from the administration of drugs such as fenfluramine[1] or levodopa.[2] Local conditions, in particular premature contacts of the teeth during occlusion and overbuilding ("high-spots") of fillings, frequently predispose to the habit. Some families are more prone to this condition than others. Initially it would probably be wise to refer this patient to her dentist. Treatment should also be directed to relieving anxiety and stress by prescribing appropriate tranquillizers: diazepam may also act as a muscle relaxant. Bruxism, if not controlled, tends to produce excessive wear of the enamel of the teeth and is often associated with increased keratinization of the occlusal line on the mucosa of the cheek. It places an additional strain on the temporomandibular joint and its associated muscles which may lead to stiffness of the muscles on waking in the morning and to temporomandibular joint dysfunction, associated with pain, clicking, and limitation of the opening of the jaws. Bruxism also tends to accelerate periodontal disease.

These harmful effects may be alleviated by the construction of a simple removable acrylic or metal splint covering the teeth of one jaw which should be worn at night after thorough cleaning of the teeth. This appliance will remove the locking effect of the cuspal interdigitation, thus allowing the patient to grind freely and distributing the occlusal forces on the supporting tissues of all the teeth rather than on a few. Occasionally the mere provision of such a splint may tend to break the habit. For this patient, if simpler forms of treatment are unsuccessful, the splint might be modified by interposing a layer of soft plastic or rubber material on its occlusal surface to eliminate the grinding noise which itself probably aggravates her anxiety.

[1] Lewis, S. A., Oswald, I., and Dunleavy, D. L. F., *British Medical Journal*, 1971, 3, 67.
[2] Magee, K. R., *Journal of the American Medical Association*, 1970, 214, 147.

Oestrogens and Male Hair Distribution

Can oestrogens be used to reduce body and facial hair in men?

It is unusual for a man to complain of excessive hair. Society accepts hairiness in men and it is rarely a problem in practice. There is considerable normal variation among different races, for example, southern and eastern Europeans are hairier than Chinese, Indians, and Negro men. A history and examination, including assessment of the distribution and quality of the hair, should enable the physician to exclude odd and unusual causes of hairiness. For example, localized hypertrichosis may be secondary to chronic skin trauma (such as biting in the mental defective) or inflammation. It might be part of a naevus or associated with diastematomyelia and may be seen on the face in porphyria cutanea tarda. Generalized hypertrichosis is a feature of some rare inherited syndromes such as dystrophic epidermolysis bullosa and Hurler's syndrome. It may accompany or follow serious illnesses (for example, carcinoma of the bronchus) and can even be attributable to drugs other than androgenic steroids such as diphenylhydantoin, streptomycin, and diazoxide. Oestrogens would have no effect on these symptomatic forms of hypertrichosis, and treatment, where possible, should be directed at the underlying disorder. Patients on systemic oestrogen therapy for cancer of the prostate develop not only gynaecomastia but also changes in body and facial hair. The body hair loses its coarseness and is decreased though not absent. Shaving may only be necessary once or twice a week. Side effects of such systemic treatment, however, prevent its use for physiological excessive hairiness and topical oestrogens are ineffective. The only justification for giving systemic oestrogens for hairiness might be in the true trans-sexualist. Full psychiatric and endocrinological assessment are essential and the patient should not expect to lose all his male pattern body and facial hair.

Positive Pregnancy Test after Termination

For how long can pregnancy tests give a positive result after either the termination of a pregnancy or a normal confinement?

The hormone on which pregnancy tests depend is human chorionic gonadotropin (HCG). There are biological variations in the amount of HCG in the blood according to the time of the pregnancy, in different individuals, and in its rate of destruction and excretion. There will be different levels of the hormone, too, in hydatidiform mole, in chorion epithelioma, and, when the chorion has died, either in utero or in the Fallopian tube. There is, therefore, no simple answer to the question, but sticking specifically to the matters asked it can be said that the ordinary pregnancy test will usually be negative after one week has elapsed. If the test is then still positive it should be repeated a week later and if still positive then further investigation by a gynaecologist is necessary.